FLINT (A.)

STERCORIN AND CHOLESTERÆMIA.

BY

AUSTIN FLINT, M. D., LL. D.,

Professor of Physiology in the Bellevue Hospital Medical College; Consulting Physician to Bellevue Hospital; Consulting Physician to the Manhattan State Hospital, etc.

REPRINTED FROM THE

New York Medical Journal

for June 5, 1897.

DR. AUSTIN FLINT'S ADDRESS BEFORE THE AMERICAN MEDICAL ASSOCIATION.

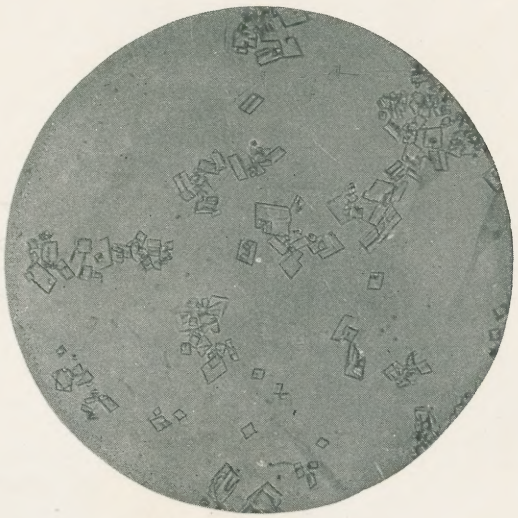

FIG. 1.—Cholesterin, 1897.

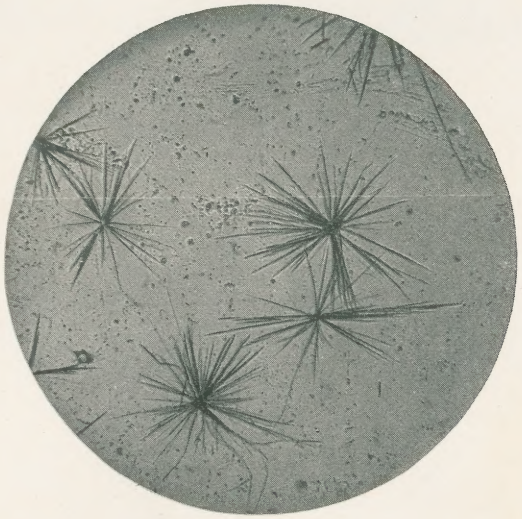

FIG. 2.—Stercorin, Flint, 1897.

FIG. 3.—Stercorin, B. and H., 1897.

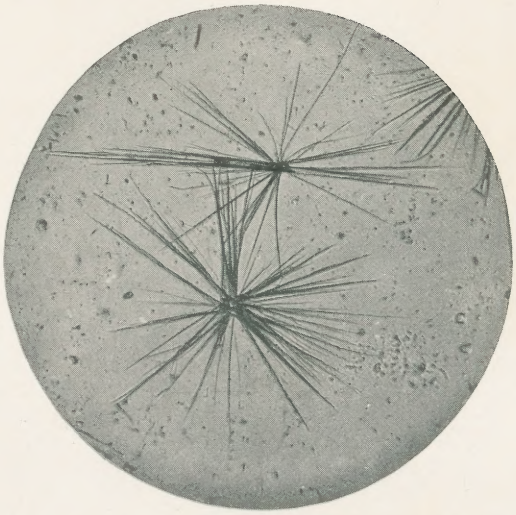

FIG. 4.—Stercorin, Flint, 1862, recrystallized in 1897.

FIG. 5.—Stercorin, Flint, original slide of 1862.

Photographs by Professor E. K. Dunham, M. D. All magnified twenty diameters.

Reprinted from the New York Medical Journal
for June 5, 1897.

STERCORIN AND CHOLESTERÆMIA.*

By AUSTIN FLINT, M. D., LL. D.,
PROFESSOR OF PHYSIOLOGY IN THE BELLEVUE HOSPITAL MEDICAL COLLEGE;
CONSULTING PHYSICIAN TO BELLEVUE HOSPITAL;
CONSULTING PHYSICIAN TO THE MANHATTAN STATE HOSPITAL, ETC.

Looking far into the future, it seems possible that our successors may fix upon the month of May, 1946, as the true centennial of the American Medical Association, dating the origin of this body from May, 1846, when a convention of representatives of our profession, held in New York, proposed the formation of a national association, which was formally organized in 1847. If your orator of to-day finds it impossible to do justice to this occasion, how much more difficult will it be to present, in a single address, an adequate picture of a full century of medical progress! The year 1946 will be the centennial of the application of anæsthesia to surgery. It will be the third jubilee of the crowning glory of the eighteenth century, the completion of the discovery of vaccination, when the terrible scourge, small-pox, which had been more destructive to human life than war or famine, was virtually subdued. At the Jenner Centenary, held in Berlin in May, 1894, Virchow stated, as an ethnological fact, that "all peoples that had not been reached by vaccination, or that had not accepted it, had disappeared from the face of the earth, destroyed by small-pox." Will the orator of 1947 be able to point to a triumph of American medicine equal to the application of anæsthesia a

* Address in Medicine delivered at the semicentennial anniversary of the American Medical Association, in Philadelphia, June 2, 1897.

hundred years before or to the beginning of an era in preventive medicine, like that inaugurated by the immortal Jenner? Looking into the future, it is possible that in fifty years small-pox will have disappeared from the face of the earth, like the peoples it has destroyed. But who can say, in the light of what has been accomplished within our own recollection, what may not be done within the next half-century? In the single line of preventive medicine, is it not possible that we may be able to secure immunity from tuberculosis, typhus and typhoid fevers, scarlatina, diphtheria, and other infectious maladies, and that these diseases may disappear? As it is now, even with a not inconsiderable popular prejudice against vaccination, many successive years have passed in the city of New York without a single case of small-pox; and medical knowledge is becoming daily more progressive and more generally accepted by the laity.

It is not too much to say that the convention of May, 1846, marked an era in the history of medical organization in the United States. It had become necessary that the medical profession should be unified and separated from those practising under sectarian designations, particularly as at least one sect was beginning to secure the confidence of men otherwise intelligent, and assumed to practise medicine on a scientific basis. Nearly coincident with the organization of this association was the discovery to which I have already alluded, which marked a grand epoch in the history of American medicine. On October 17, 1846, practically the first surgical operation was performed under the influence of an anæsthetic administered by inhalation. Its semicentennial has recently been most impressively celebrated at the Massachusetts General Hospital, in Boston. There are few who remember the horrors of severe surgical operations and the agonies of difficult childbirth before anæsthesia, as there are few remaining who participated in the convention which organized what is now the American Medical Association; but all can realize what surgery would be without artificial insensibility to pain, and what the medical profession would be without a national association.

The status of medicine forty years ago is quite within my recollection. Medicine is not, never was, and never will be an exact science; but it always has been progressive, and never more so than at the present time. Fifty years ago, perhaps medicine merited the reproach of being the least exact of all sciences; but its progress within the last fifteen years has been so prodigious that it is now in advance of them all. The Abbe illuminating apparatus made the study of bacteria possible; and this, with the wonderful apochromatic lenses, as it now appears to us, have rendered nearly perfect our technical means of histological and bacteriological research. We no longer differentiate and separate structures by the coarse methods of actual dissection alone, but with the delicate and precise instruments used in cutting thin sections and by staining, we have come to an exact knowledge of physiological and pathological histology, which, fifty years ago, seemed unattainable. Without staining fluids, the physiological and pathological histology of the present day would be impossible. Fifty years ago, skill in the diagnosis of certain diseases was acquired only by long practice and large experience. With our present methods, properly employed, it is impossible to make an error in the diagnosis of many of the diseases which formerly presented difficulties, such as typhoid fever, tuberculosis, diphtheria, cholera and most of the neoplasms. To say that pathology has been revolutionized within the last ten or fifteen years is not enough—a new pathology has been created, and with it have come an intelligent hygiene, prevention and therapeutics, based upon exact scientific knowledge.

Eleven years ago the great physician whose name I bear, and who still lives in the memory of this association, wrote an address which was to have been delivered before the British Medical Association, entitled Medicine of the Future. This classic legacy to the profession he so loved and adorned embodied recollections of a half-century of medical observation, with a prophetic view of the possibilities of medicine within the succeeding half-century. It was difficult for this wise physician to restrain his

predictions within the bounds of reasonable enthusiasm. The epoch-making discovery of the bacillus tuberculosis, announced by Koch in 1882 and graphically described and illustrated by Dr. Belfield before this association, at the meeting of 1883, made a most profound impression upon his mind and imagination, which found expression in an elaborate paper on the subject read in January, 1884. His predictions of possibilities in medicine before 1936 are now more than verified. It was predicted that "before the lapse of another half-century there will be another era in organic chemistry, and that light will penetrate dark recesses which histology can not reach." If "light" be taken in its literal sense, is not this more than realized by Röntgen's marvelous discovery, in which a hitherto unknown light is made to penetrate opaque matter and disclose the invisible? In 1886, he wrote: "Moreover, there are present intimations of important discoveries respecting inoculation with attenuated viruses and contagia in order to forestall the development of infectious diseases. Here open up to the imagination the future triumphs of preventive medicine in respect to all classes of disease." Now, little more than ten years later, serum therapy has taken a permanent place in practice, and we stand on the threshold of a full knowledge of immunity, natural and acquired.

As no human imagination fifty years ago could have pictured the condition of the medicine of to-day, so it to-day seems impossible to imagine the progress of another half-century. Never, since medicine became a science, has medical history been made so fast as now. Between the time of writing and of delivering this address, scientific labor may give birth to a discovery destined to revolutionize some department of medicine, as Pasteur, Koch and their followers have revolutionized therapeutics, and as Lister has created a new surgery.

The reasonable limits of an anniversary address do not permit even an enumeration of the greatest of the advances in the science of medicine since the organization of this association, much less their discussion. Your orator on surgery will find it impossible adequately to

describe the progress of the last half-century in a single address; your orator on state medicine can hardly compass the wonderful advances made even in the single line of prevention of disease; and I certainly can not hope to be more successful.

It is a matter of congratulation that the name of this body was early changed from National to "American Medical Association." We have good reason to be proud of American medicine, and our great representative association may properly claim a distinctive title. When one is able to call up at random the discoveries in gastric digestion, anæsthesia in surgery and obstetrics, the successful deligation of the arteria innominata, the operation for vesico-vaginal fistula, ovariotomy, and intestinal anastomosis, to say nothing of minor advances in medicine and surgery, can we not claim a distinctive place for American medicine? It is in the United States that advances in the science of medicine find the most ready acceptance and appreciation. The American physician is the most intelligent and judicious therapeutist; and in the United States are the best and safest surgery and gynæcology.

I hope to see, beginning with the second half-century of the American Medical Association, a more complete unity of the profession, through its authority and influence. In the matter of general professional welfare, there seems to me nothing more important than uniformity in medical legislation, and, so far as possible, in educational requirements preliminary to the study of medicine and for license to practise after graduation. Admitting the proposition that the profession is crowded, it is evident that this condition is most serious in the large cities; but overcrowding can not be prevented by legislative enactment, except in so far as unqualified men are excluded. Uniformity of legal qualifications to practise medicine in the different States can best be secured by making every State society actually, as well as nominally, a branch of the American Medical Association, with permanent committees from each State organization together to constitute a central legislative body. The object of this central body should be to secure uniform medical laws in all the States,

making any State license valid for all, and a matriculation certificate for one State good for matriculation in all schools represented in the Association of American Medical Colleges. A certain kind of medical instruction must be concentrated in large cities, where clinical material is abundant; and absolute uniformity of curriculum can not exist in all colleges; but certainly the legal requirements for practice, as determined by examination by State boards, can be made practically identical for all the States. While this would not prevent ambitious young men from trying their fortunes in large cities, it would distribute well-qualified physicians more equally in the country at large and tend to raise the standard of qualifications and usefulness of the average country doctor.

It is the prerogative of the presiding officer of this association to make recommendations, and this is not the province of one appointed simply to give an anniversary discourse. At the jubilee meeting to be held later in the session, it is hoped that the four surviving members of the convention of 1846 will be present. From at least one of these you may expect a more accurate and complete account of the past work of the association and a more intelligent view of its probable future than I am able to give. What I have had the honor to present I well know is entirely inadequate to the occasion, and it has been given merely as an introduction to addresses by others, which will be much more suitable and interesting. The remainder of the time that has been placed at my disposal I shall venture to occupy with a subject which I hope may not prove entirely unworthy of your attention.

Stercorin and Cholesterœmia.—While the presentation, on this occasion, of researches made and published thirty-five years ago—viewing the question from a physiological standpoint—calls for an explanation and perhaps an apology, none is required if their great importance in relation to the pathology of the liver is considered, especially as cholesterœmia is by no means accepted as a distinct pathological condition. Were it not that stercorin has just been rediscovered in Germany by two eminent physiological chemists, who make no mention of its full

description in 1862 and have even called it by another name, I probably should not have repeated and extended my original observations. As it is, however, I feel that I may properly, as an American investigator, make my reclamation before the American Medical Association. Although my paper, published in the *American Journal of the Medical Sciences* in October, 1862, received an "honorable mention" and substantial recognition from the Institute of France, and my observations have been verified and extended by French and German investigators, many writers on physiology and pathology, even the most recent, fail to recognize such a substance as stercorin and, in treating of cholesterin, speak of its function as obscure or unknown.* In *An American Text-book of Physiology*, Philadelphia, 1896, cholesterin is described as a constant constituent of the bile, very widely distributed in the body, and eliminated by the liver cells from the blood. "That it is an excretion is indicated by the fact that it is eliminated unchanged in the fæces." Stercorin is not mentioned. As a matter of fact, cholesterin does not occur in the human fæces in health, and its presence in this situation is exceptional.

In Hoppe-Seyler's *Zeitschrift für physiologische Chemie*, Strassburg, 1896, is a paper by Bondzynski and Humnicki entitled The Destination of Cholesterin in the Animal Organism. The authors profess to have discovered a new constituent of the human fæces, which they call "koprosterin." This substance is identical with stercorin, fully described in 1862. The reading of this article led me to repeat the original researches of 1862, carrying them out by the methods then employed, at the same time repeating the observations of Bondzynski and Humnicki with the methods and appliances used in their work. It is mainly an account of these new observations that I now give. The chemical manipulations were done by Dr. H. A. Haubold, assistant to the chair of physiology in the Bellevue Hospital Medical College, and J. A. Mandel, assistant in the department of chem-

* Foster. *A Text-book of Physiology*, New York and London, 1895, p. 356.

istry in the College of the City of New York and to the chair of chemistry in the Bellevue Hospital Medical College. To these two skillful assistants I am indebted for most painstaking and accurate work extending over a period of several months.

The original stercorin, of which specimens obtained in 1862 are in my possession, was extracted from the human fæces by the following process: The dried and pulverized fæces were extracted with ether. The ethereal extract was passed through animal charcoal and afterward evaporated. The residue was then extracted with boiling alcohol. The alcoholic extract was treated with potassium hydrate solution, at a temperature near the boiling point of water, in order to remove the fats by saponification, which were washed out with water until the filtrate was neutral and perfectly clear. The filter was dried, extracted with ether, and the ethereal extract evaporated to dryness and extracted with boiling alcohol. The stercorin was obtained from the alcoholic extract by repeated crystallization.

This process was exactly repeated in our recent observations, and, at the same time, stercorin was extracted by the process described by Bondzynski and Humnicki. Normal human fæces were obtained to the amount of about fifty pounds. After drying, the fæces were divided. Two analyses each were made by Haubold and Mandel, each one extracting stercorin in one portion by the original method, and in the other by the new method. All the extracts obtained were identical in their composition, reactions and the form of crystals. It was fortunate that I had for comparison a fairly large specimen of stercorin extracted in 1862, and a microscopic slide bearing the date of June, 1862, in which the crystals were perfect. The product obtained by my process was a little more abundant and crystallized rather more readily than that obtained by the later method.

In the process employed by Bondzynski and Humnicki, the dried fæces were extracted with ether, using Soxhlet's extraction apparatus. The fats were saponified with sodium alcoholate. No animal charcoal was used.

The substance was purified by repeated crystallizations. These variations from the original method are unimportant, except in so far as they expedite the process of extraction. The form of the crystals and the reactions were identical with those which I obtained for stercorin in 1862. Analyses of the products obtained by us, full details of which are given in a paper sent to Hoppe-Seyler's *Zeitschrift*, gave, for stercorin, the formula, $C_{27}H_{48}O$, the formula found for cholesterin being $C_{27}H_{46}O$. The change of cholesterin into stercorin is effected by the addition to the former of two atoms of hydrogen. A close comparison of the results of our ultimate analyses with those obtained by Bondzynski and Humnicki shows conclusively that "koprosterin" and stercorin are identical, and that stercorin is not an impure cholesterin, as is held by some eminent investigators, such as Hoppe-Seyler, K. B. Hofmann, and others. Stercorin crystallizes in long, fine needles which radiate from a centre, forming tufts, and which can not be confounded with the characteristic crystals of cholesterin. In a chloroform solution, stercorin gives, with an equal volume of concentrated sulphuric acid, first a yellow color and then a gradual change to orange, red and finally dark red. Treated in the same way, cholesterin promptly gives a blood-red reaction without these intermediate tints.

The opinion expressed by Hoppe-Seyler, Hofmann, and indeed many others, that stercorin simply is impure cholesterin, can not have been based upon a practical knowledge of this substance. Stercorin has a well-defined formula—$C_{27}H_{48}O$—which has been calculated and verified by the formation of esters. Its crystals are quite different from crystals of cholesterin and are invariable in form, arrangement, and color. It was extracted by methods practically the same as those used in the extraction of cholesterin. In view of these facts, to assume that stercorin is an impure substance one must deny a positive scientific basis to organic chemistry.

In the recent, as well as in the original observations it was clearly shown that cholesterin was changed into stercorin in passing down the intestinal canal. I found

that this change involved processes incidental to intestinal digestion. Cholesterin and no stercorin was found in the fæces of fasting animals and in the meconium. Bondzynski and Humnicki found an increased proportion of "koprosterin" in human fæces after the ingestion of a certain quantity of cholesterin. They also showed that cholesterin united readily with bromine, while "koprosterin" formed no such combination; and, indeed, by the use of bromine, these two substances may be separated when they exist together. They confirmed the empirical formula for their product by the formation of a number of esters.

In 1862, I wrote: "What the discovery of the function of urea has done for diseases which now come under the head of uræmia, the discovery of the function of cholesterin may do for the obscure diseases which may hereafter be classed under the head of cholesterænia."

It is now generally admitted that the bile, in addition to its function connected with digestion, contains one or more excrementitious matters. Taking into consideration the various ingredients of the bile, there seems to be but one which can logically be compared to urea. Cholesterin is found in many of the tissues and organs of the body and exists in the blood. Likening it to urea, it becomes a question whether it is formed in the liver and discharged in the bile or is merely separated from the blood by the liver and excreted. As it is constantly found in notable quantity in the nervous tissue, in the proportion of eight to twelve parts in a thousand, it occurred to me to examine the blood of the internal jugular and compare the proportion of cholesterin with that found in arterial blood. In one experiment on a dog, the blood being taken without using an anæsthetic, I found an increase in the jugular over the carotid of nearly sixty per cent. In an etherized animal the increase was only about three and a half per cent. In another dog, not etherized, the increase was about twenty-three per cent. There was also an increase of from four to six per cent. in the blood of the femoral vein over arterial blood. In three cases of hemiplegia, the blood from the arm of the sound side

contained about the normal proportion of cholesterin, while blood from the affected side contained no cholesterin.

In an experiment on a dog it was found that the arterial blood lost about twenty-three per cent. and the portal blood about four and a half per cent. in passing through the liver, comparing these two kinds of blood with blood taken from the hepatic vein.

These experiments led to an examination of the fæces to determine the quantity of cholesterin discharged; but in a number of careful examinations of many different specimens of fæces I was unable to find cholesterin. I found, however, what appeared to be a non-saponifiable fatty substance in considerable quantity. Examining this substance daily with the microscope, after five or six days I saw crystals beginning to form, which finally presented the appearances I have already described as characteristic of stercorin. I found the daily discharge of stercorin to be 0.7 gramme, about equal to the estimated quantity of cholesterin discharged into the intestine in the bile in the twenty-four hours. In but one examination of fæces of the dog did I find cholesterin, and this was in a fasting animal, a small quantity of cholesterin being found with stercorin. In a specimen of meconium, I found a hundred and sixty parts in a thousand of cholesterin and no stercorin. In clay-colored fæces from a patient with jaundice from obstruction, neither cholesterin nor stercorin was found. In the fæces of the same patient, which were normal in color and obtained fifteen days after the first examination, stercorin was found and no cholesterin. These experimental facts seemed to show that the stercorin of the fæces was derived from the cholesterin of the bile, and that the change of cholesterin into stercorin was incidental to the processes of intestinal digestion. In no case was I able to detect in the fæces any trace of the biliary salts.

Passing from these observations to the pathological relations of cholesterin, after examining three specimens of normal blood and finding the proportion of cholesterin from 0.445 to 0.751 of a part in a thousand, examinations

were made of the blood of patients with simple jaundice and those with what is called icterus gravis, the cases terminating fatally with grave nervous symptoms. In a case of simple jaundice, terminating in recovery at the end of about four weeks, the blood contained 0.508 of a part in a thousand, well within the limits in normal blood. In a case of jaundice with cirrhosis, terminating fatally with serious nervous disturbance, the blood taken six days before death contained 1.850 part in a thousand of cholesterin, an immense increase over the normal proportion. In this case, on post-mortem examination, the liver was found contracted, and the gall bladder was shrunken, containing only about seven cubic centimetres of bile.

The question of cholesteræmia has been much discussed since 1862, for the most part with scant approval or without acceptance. However, Picot,* in 1872, reported a fatal case of "grave jaundice" in which he determined a great increase in the proportion of cholesterin in the blood, 1.804 part in a thousand. Many attempts have been made, also, to produce toxic effects by injecting cholesterin into the blood, but most of them have been unsuccessful on account of mechanical obstruction of the blood-vessels. In 1873, however, Koloman Müller † succeeded by injecting cholesterin rubbed with glycerin and mixed with soap and water. In five experiments on dogs, injecting in each 0.045 gramme of cholesterin, he produced a complete representation of the phenomena of "grave jaundice."

In repeating the original researches of 1862, the observations, as regards analysis of fæces, etc., were somewhat extended. With modern apparatus, the manipulations may be freed from many disagreeable features which heretofore, probably, have interfered with this line of investigation. In extracting stercorin, various volatile fatty acids and other substances were removed, the constitution and relations of which are unknown. We

* *Journal de l'anatomie*, Paris, 1872, tome viii, p. 246 *et seq.*

† Ueber Cholesterämie. *Archiv für experimentelle Pathologie und Pharmakologie*, Leipzig, 1873, Bd. i, S. 213 *et seq.*

studied, in this connection, some of the products of bacterial action, obtaining, by the action of fæcal bacteria on proteids, skatol and indol, both substances containing nitrogen. It is well known that phenol and cresol also exist in the fæces. These nitrogenized matters are putrefactive products, nothing is known of their physiological or pathological relations, and up to this time stercorin is the only excrementitious matter yet found in the fæces the origin and relations of which are at all understood. Our knowledge, indeed, of the physiological chemistry of the fæces is only just begun; and we may look to future investigations for much that will be most important as well as interesting. The same may be said, in a measure, of the bile and of the true pathology of certain functional and structural diseases of the liver. How long shall we continue to speak of biliousness, congestion or torpor of the liver, the classic "liver complaint," *et id genus omne*, using terms which have no scientific meaning? Undoubtedly there are general disturbances, dependent upon some disorder in the functions of the liver, which occur without jaundice, and this fact has long been recognized. In a case of cirrhosis with considerable constitutional disturbance but no jaundice, the blood was found to contain an excess of cholesterin, 0.922 of a part in a thousand. In what is termed acholia, there may be grave nervous symptoms without jaundice, and the pathology of such cases is unknown. The biliary salts are not found in the blood, and the symptoms can not be accounted for by disturbances in digestion. It is possible that light will be shed upon their pathology if it is admitted that there is a condition called cholesteræmia. As yet this is but speculation; but if the theory of cholesteræmia is accepted, a wide field of inquiry is opened in this direction, and ere long we may speak of "biliousness" and "liver complaint" with some definite ideas of their pathology.

It must be remembered that the liver is by far the largest gland in the body; that it secretes a fluid which is known to have a double function, one connected with digestion and the other with the elimination of choles-

terin; that the blood from the digestive tract all passes through this organ, where it undergoes certain changes; that it probably stores up the products of amylolytic digestion in the form of glycogen; that it arrests certain poisons, and that it is the chief organ concerned in the production of urea, which is discharged by the kidneys. It may have other uses in what is now called internal secretion, in addition to that of destruction of blood-corpuscles and the change of hæmoglobin into bilirubin. With all these known varied uses of the liver, however, the pathology of hepatic diseases is most obscure. We do not know, even, the cause and mechanism of the formation of gallstones, which are often composed almost entirely of cholesterin.

The term acholia, as used in pathology, now means very little and conveys no distinct idea of the causes of the nervous symptoms which attend this condition. The term cholæmia is generally regarded as almost synonymous with jaundice. If cholesteræmia is recognized as a distinct pathological condition, with symptoms due either to the accumulation of cholesterin in the blood, acting as a toxic substance, or to imperfect separation of cholesterin from the nervous tissue, a positive advance will be made in our knowledge of the pathology of many obscure liver disorders.

The quantitative estimation of cholesterin in the blood is not difficult, and it does not require more than from four to six or eight grammes of blood. The only tedious manipulations are the drying, saponification and weighing; and these are readily done in a well-appointed laboratory. Some process may be devised which will expedite this extraction. If examinations of the blood were to be made in cases of obscure nervous disturbance, in epilepsy and other disorders of this nature, it is possible that cholesterin may be found to play an important part in their pathology. The fact that bromine readily combines with cholesterin, taken in connection with the wide use of the bromides in diseases of the nervous system, is very suggestive. May not the bromides promote the elimination of cholesterin, a substance which is

so insoluble and which forms few combinations? These points seem well worthy of the consideration of pathologists and therapeutists. Certainly the physiological and pathological relations of cholesterin offer a wide and perhaps fruitful field for further observation.

With this paper I present photographs of cholesterin, stercorin extracted by the original method, and stercorin extracted by the method of Bondzynski and Humnicki, all in 1897, with a photograph of crystals obtained in 1897 from a specimen of stercorin extracted in 1862.

I have added, for comparison with the recent crystallization from the specimen of 1862, a photograph from a slide marked June, 1862. These crystals, which are from the same specimen of 1862, have been mounted for thirty-five years and are much more abundant and beautiful than those obtained by recrystallization in 1897.